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CLINICAL RESEARCH
Endocarditis

The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis

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Aims To determine whether the timing of surgery could influence mortality and morbidity in adults with complicated infective endocarditis (IE).

Methods and results In 291 consecutive adults with definite IE who underwent surgery during the active phase, we compared those operated on within the first week of antimicrobial therapy ($n = 95$) to those operated on later ($n = 191$). The impact of the timing of surgery on 6-month mortality, relapses, and postoperative valvular dysfunctions (PVD) was analysed using propensity score (PS) analyses. After stratification of the cohort into quintiles based on the PS, ≤1st week surgery was associated with a trend of decrease in 6-month mortality in the quintile of patients with the most likelihood of undergoing this early surgical management [quintile 5: 11% vs. 33%, odds ratio (OR) = 0.18, 95% CI (confidence interval) 0.04–0.83, $P = 0.03$]. Patients of this subgroup were younger, were more likely to have *Staphylococcus aureus* infections, congestive heart failure, and larger vegetations. Besides, ≤1st week surgery was associated with an increased number of relapses or PVD (16% vs. 4%, adjusted OR = 2.9, 95% CI 0.99–8.40, $P = 0.05$).

Conclusion Surgery performed very early may improve survival in patients with the most severe complicated IE. However, a greater risk of relapses and PVD should be expected when surgery is performed very early.

Keywords Endocarditis • Surgery • Mortality • Prognosis

Introduction

The number of patients operated on during the active phase of infective endocarditis (IE) has increased during the last decade and ranges from 30% to 60%.[1,2] Recent changes in the epidemiological profile of the disease could explain this trend, with an increase in complicated situations owing to a greater incidence of more virulent microorganisms and intracardiac material infections.[3–5] Moreover, the development of surgical techniques and publications of large studies demonstrating the beneficial effect of surgery in complicated endocarditis[6–8] have encouraged physicians to offer surgical treatment to an increasing number of patients. However, not only does the effect of surgery not seem to be uniform in all patients,[8–10] but uncertainties remain about the optimal timing of the operation. Although the indications for surgery are well-defined in the international guidelines,[11–13] no consensus exists on the optimal timing of surgical treatment during the active phase of infection because of a lack of evidence-based data. A recent study addressed this subject but did not find an independent effect of the timing of surgery on mortality, and it did not analyse its impact on the subsequent risk of relapses or

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postoperative valvular dysfunctions (PVD), which are concerns when material is implanted into infected tissues.[14]

Therefore, taking advantage of a larger, prospectively enrolled cohort of patients with IE, we assessed whether the timing of surgery during the active phase of infection influenced 6-month mortality and the risk of relapses and PVD using a propensity analysis to control for bias in treatment selection. We hypothesized that surgery performed very early could reduce mortality without a high risk of postoperative relapses and valvular dysfunction.

Methods

Patient sample

All consecutive patients admitted to our centre between January 1992 and June 2007 with a definite diagnosis of IE[15] were eligible and prospectively included in our database. For IE cases included before 2000, when the modified Duke criteria were introduced, we screened the case histories and applied the new case definition retrospectively. Patients with only pacemaker or defibrillator IE were excluded. The study group was composed only of patients ≥18 years old who underwent operations during the course of antimicrobial therapy (active phase). This study was approved by our ethics committee and informed consent was obtained from all patients.

Baseline data

Clinical data, blood cultures, and serologies were systematically collected at the time of surgery. Direct analysis and polymerase chain reaction were performed on each valve explanted after 1994. All patients underwent both transthoracic and transoesophageal echocardiograms in our laboratory within 48 h before surgery or in the operating theatre. The degree of aortic and mitral regurgitation was assessed semi-quantitatively or by quantitative methods and classified as mild, moderate, or severe.[16] Vegetation maximal length was measured as previously described.[17] Diagnosis of abscess with or without fistula was suspected in front of a thickened area or mass with heterogeneous echogenic or echolucent appearance.[18] The data were electronically stored and used as noted at the time of the original examination, without alteration.

Surgical data

Surgery was performed during the course of the appropriate antimicrobial therapy and was indicated for at least one of the following three conditions, which were in accordance with the current guidelines (major indications):[11–13] (i) haemodynamic impairment, including CHF, or severe left valvular regurgitation without CHF but with evidence of elevated end-diastolic or left atrial pressures; (ii) high embolic risk owing to emboli with persistent >10 mm vegetation, or >15 mm vegetation without emboli; (iii) presence of an abscess with or without fistula or pseudo-aneurysm. All the patients with persistent bacteraemia after 7 days of antimicrobial therapy had at least one of the previous indications for surgery. In the case of ischaemic stroke, diagnosis was confirmed by an experienced neurologist and a cerebral computed tomography scan was performed systematically 24 h before surgery, to ensure the absence of haemorrhage. In cases of coma, the decision to operate was made according to the neurological prognosis, comorbidities, and the severity of the haemodynamic impairment. During the operation, when the infection was limited to the cusps of the native aortic valves or to the leaflets of the aortic prostheses, the surgery consisted of simple valve replacement by conventional prostheses or of implantation of an aortic homograft, at the discretion of the surgeon. Whenever infection extended to surrounding structures, or in the case of annulus abscess with annulus disruption, surgery consisted of an extensive resection of all infected tissues and their reconstruction by either glutaraldehyde-fixed autologous or bovine pericardium, Dacron® fabrics, or aortic homograft. In cases of mitral localization, repair was always preferred when possible, most often with excision of vegetation and reconstruction with autologous pericardium.

Endpoints

The endpoints were 6-month mortality and a combined endpoint including the rate of IE relapses or PVD at 6 months. PVD were diagnosed by echocardiography and included valve repair failures and moderate or severe prosthesis dysfunctions not related to IE relapse. The baseline was defined as the date of surgery. Postoperative events were collected during routine follow-up visits or by contacting the patients' physicians and systematic echocardiograms.

Statistical analysis

To assess the impact of the timing of surgery, we chose to analyse the time between the beginning of the appropriate antimicrobial therapy and surgery as a continuous variable and as a categorical variable with a cut-off of 7 days. This cut-off was chosen according to clinical practice and the data from previous studies[19,20] and guidelines[11–13] showing a higher risk of embolism during this time and a failure of medical treatment when bacteraemia persists after 1 week. Therefore, two groups of patients were formed according to the timing of surgery: the '≤1st week surgery group' and the '>1st week surgery group'.

Since patients were not randomly assigned to one of these two surgical groups, we adjusted for factors favouring selection of ≤1st week surgery using propensity score (PS) in order to reduce the selection bias.[21] With 25 baseline variables at the time of surgery [age, sex, diagnosis year, comorbidity index >2,[23] serum creatinine >2 mg/dL, IVDA, early prosthetic valve IE, prosthetic valve IE, IE location (mitral, aortic, mitro-aortic, tricuspid), CHF, embolic event, cerebral embolism, stroke, cerebral haemorrhage, Glasgow coma scale, abscess, vegetation length (continuous, >10 mm, >15 mm), LVEF < 45%, negative blood cultures, and type of microorganism] and clinically plausible interaction, a PS of undergoing ≤1st week surgery was estimated for each patient using an extensive logistic regression analysis. This score reflected the probability that a patient would undergo ≤1st week surgery. To more fully identify a subgroup of patients who would benefit from ≤1st week surgery, the entire study group was secondary stratified into quintiles of equal size based on the estimated PS, as previously described.[8,22]

The impact of the timing of surgery on 6-month mortality, relapses, and PVD was then assessed (logistic regression) in the entire group after adjustment for PS quintiles and in each quintile. Linearity assumption was assessed using Box–Tidwell test and model adequacy was verified using Hosmer–Lemeshow test.

Differences among the different groups were compared using the χ^2 test or Fisher exact test for categorical variables; the unpaired *t*-test, the Mann–Whitney *U* test, or Kruskall–Wallis test were used to compare continuous variables. A two-sided *P*-value of <0.05 was established as the level of statistical significance for all tests. All analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Among 534 consecutive patients admitted with a definite diagnosis of IE, 342 (64%) had at least one indication for surgery. A total of 321 patients (60%) were referred by another hospital. Fifty-one patients (10%) were excluded because they did not undergo surgery until after the end of antimicrobial therapy ($n = 44$) or were denied surgery because of excessive operative risk ($n = 5$) or because they refused the procedure ($n = 2$). The 291 patients (55%) operated on during the course of antimicrobial treatment formed our cohort, with 95 patients in the '≤1st week surgery group' and 196 in the '>1st week surgery group'. No patient initially included was excluded from analyses after initial assessment. *Tables 1* and *2* display the characteristics of groups.

In the '≤1st week surgery group', indications for surgery were haemodynamic impairment in 75 patients (79%), including five with a cardiogenic shock, high embolic risk in 56 (59%), presence of abscess in 40 (42%), and more than one indication in 61 (64%). Surgery in this group was performed at a median time (interquartile range) of 3 days (1–5) after the beginning of antimicrobial treatment. In the '>1st week surgery group', indications for surgery were haemodynamic impairment in 151 patients (79%), none with cardiogenic shock, high embolic risk in 96 (50%), presence of an abscess in 72 (37%), and more than one indication in 110 (58%). Surgery in this group was performed at a median time (interquartile range) of 19 days (12–32) after the beginning of antimicrobial treatment.

Propensity score

The propensity model yielded a concordance index (*c* index) of 0.82 [95% confidence interval (CI), 0.77–0.87], indicating a good ability to differentiate between patients according to the surgical strategy (≤1st week surgery vs. >1st week surgery). The distribution of the PS between the two groups, '≤1st week surgery group' vs. '>1st week surgery group', was 0.24 ± 0.20 vs. 0.51 ± 0.23 ($P < 0.001$), respectively. The adjustment for PS quintiles adequately balanced the groups for the baseline variables (*Tables 1* and *2*).

Impact of the timing of surgery on 6-month mortality

The 6-month mortality was 13% (37/291) (*Table 3*). The causes of death were multiorgan failure, severe CHF, or septic shock in 27 patients, complicated IE relapses in four patients, stroke in two patients, myocardial infarction in two patients, irreparable

Table 1 Clinical, laboratory, and echocardiography findings of the 291 patients with infective endocarditis operated during antimicrobial therapy

	≤1st week surgery group (n = 95)	>1st week surgery group (n = 196)	Unadjusted P-value	Propensity score adjusted P-value
Age (mean ± SD, years)	53 ± 16	58 ± 15	0.01	0.89
Male sex	69 (73)	155 (79)	0.22	0.81
Comorbidity index >2	33 (35)	48 (25)	0.07	0.84
HIV infection	1 (1)	4 (2)	1.0	0.20
History of cancer	13 (14)	20 (10)	0.38	0.84
Diabetes	9 (10)	29 (15)	0.21	0.13
Serum creatinine >2 mg/dL	12 (13)	37 (19)	0.18	0.96
Intravenous drug abuse	12 (13)	10 (5)	0.02	0.74
CHF	44 (46)	78 (40)	0.29	0.92
Embolic event	31 (33)	94 (48)	0.01	0.89
Stroke	10 (11)	27 (14)	0.44	0.98
Cerebral haemorrhage	2 (2)	9 (5)	0.51	0.75
Glasgow coma scale (mean, [min])	14.9 (8)	14.8 (3)	0.46	0.80
Valve localization				
Prosthetic valve	20 (21)	60 (31)	0.09	0.80
Aortic	61 (64)	137 (70)	0.33	0.92
Mitral	50 (53)	98 (50)	0.67	1.0
Mitro-aortic	18 (19)	43 (22)	0.56	0.92
Early prosthetic valve IE	2 (2)	2 (1)	0.30	0.75
Vegetation	77 (81)	156 (80)	0.77	0.54
Vegetation length [median, (interquartile range), mm]	11 (5–17)	15 (6–19)	0.13	0.95
Abscess	40 (42)	72 (37)	0.38	0.92
LVEF < 45%	2 (2)	4 (2)	1.0	0.99

CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

Table 2 Microbiological findings of the 291 patients with infective endocarditis operated during antimicrobial therapy

	≤1st week surgery group (*n* = 95)	>1st week surgery group (*n* = 196)	Unadjusted *P*-value	Propensity score adjusted *P*-value
Negative blood cultures	17 (18)	29 (15)	0.50	0.93
Microorganisms				
Staphylococcus aureus	23 (24)	25 (13)		
Coagulase-negative staphylococci	5 (5)	19 (10)		
Viridans streptococci	17 (18)	35 (18)		
Streptococcus bovis	13 (14)	39 (20)	0.21	0.23
Enterococci	12 (13)	21 (11)		
Others	14 (15)	32 (16)		
No microorganism identified	11 (12)	25 (13)		

Values are expressed as number (%).

Table 3 Outcome of the 291 patients with infective endocarditis operated during antimicrobial therapy

	≤1st week surgery group (*n* = 95)	>1st week surgery group (*n* = 196)	*P*-value
6-month mortality	14 (15)	23 (12)	0.47
Relapses and postoperative valvular dysfunction	15 (16)	7 (4)	0.0005
Relapses	8 (8)	4 (2)	0.02
Postoperative valvular dysfunction	7 (7)	3 (2)	0.02

Values are expressed as number (%).

abscess in one patient, and unknown in one patient. After adjustment for PS quintiles, no significant effect of ≤1st week surgery was observed on 6-month mortality in the entire cohort [15% vs. 12%, adjusted odds ratio (OR) = 1.3, 95% CI 0.55–3.06, $P = 0.55$] as well as when the timing of surgery was tested as a continuous variable (adjusted OR = 1.0, 95% CI 0.98–1.02, $P = 0.86$). After stratification into quintiles, ≤1st week surgery was associated with a trend of a decrease in 6-month mortality in the quintile of patients with the most likelihood of undergoing this strategy (quintile 5: 11% vs. 33%, OR = 0.18, 95% CI 0.04–0.83, $P = 0.03$, *Figure 1*). PS quintiles were not significantly associated with 6-month mortality ($P = 0.51$) but the interaction between PS quintiles and ≤1st week surgery was statistically significant ($P = 0.021$). Moreover, there was a significant interaction between PS 5th quintiles and ≤1st week surgery (adjusted OR = 0.078; $P = 0.004$).

In the other quintiles, a non-significant trend of an increase in 6-month mortality was observed with ≤1st week surgery, except in quintile 1 in which none of the patients had this strategy. However, a trend towards a decrease of mortality with ≤1st week surgery was observed from the quintile 2 to the quintile 5 (*Table 4*).

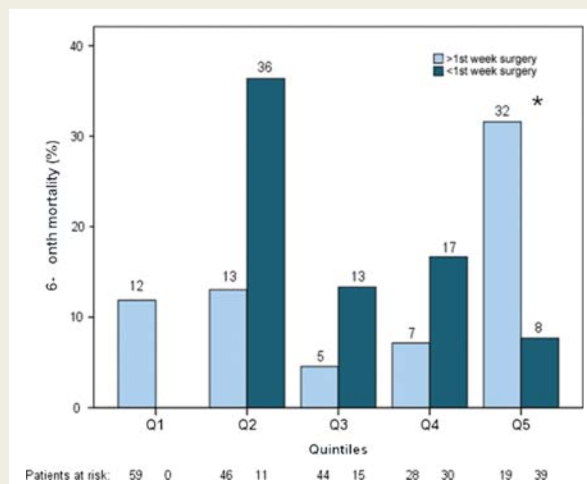

Figure 1 Six-month mortality according to propensity subgroups (Q = quintile). *In quintile 5, ≤1st week surgery was associated with reduced 6-month mortality (odds ratio = 0.18; 95% CI 0.04–0.83; $P = 0.03$). Values are expressed as number (%).

In comparison with the other subgroups, the patients in quintile 5 were younger ($P < 0.0001$), were more likely to have *Staphylococcus aureus* IE ($P < 0.0001$), CHF ($P = 0.027$), and larger vegetations (continuous, $P = 0.006$; >10 mm, $P < 0.0001$; >15 mm, $P < 0.0001$; *Table 5*).

Impact of the timing of surgery on 6-month relapses and PVD

The rate of relapses and PVD at 6 months was 8% (22/291) (*Table 3*). After adjustment for PS quintiles, ≤1st week surgery was associated with a trend towards an increase of relapses and PVD in the entire cohort (16% vs. 4%; adjusted OR = 2.9; 95% CI 0.99–8.40; $P = 0.05$). These postoperative events required re-operation in 53% (8/15) of patients in the '≤1st week surgery group' vs. 43% (3/7) in the '>1st week surgery group'. In quintile 5, 11 patients (19%) had relapses or PVD.

Discussion

To our knowledge, this is the first observational study that is designed to limit selection bias and suggests a significant impact of the timing of surgery on mortality in IE. In this contemporary and large cohort, the impact of the timing of surgery was not uniform and the ≤1st week surgical management was associated with a reduced 6-month mortality in the subset of patients with the most indications for undergoing this strategy. Therefore, our propensity analysis suggests that patients who are operated on within the 1st week of antimicrobial therapy are most likely to derive substantial mortality reduction benefits when they are relatively young with *S. aureus* IE complicated by heart failure and large vegetations. However, ≤1st week surgery was associated with a trend to a higher risk of relapses or PVD at 6 months.

Timing of surgery and mortality

Despite several recent advances in diagnosis and treatment, IE still poses a serious risk for major morbidity and death. Successful management will require combined medical/surgical treatment in cases of major complications or predictors of poor outcome.[24]

Table 4 **Logistic regression results on the impact of ≤1st week surgery on 6-month mortality by propensity subgroups (quintiles)**

	Odds ratio	95% CI	*P*-value
Q1	NA	NA	NA
Q2	3.8	0.85-17-04	0.08
Q3	3.2	0.41–25.3	0.26
Q4	2.6	0.46–14.7	0.28
Q5	0.18	0.04–0.83	0.03

NA, not applicable because of the absence of patients in the ≤1st week surgery group.

A haemodynamic impairment, a high risk of embolism, and an abscess are the three major conditions where an indication to perform urgent surgery may be discussed. CHF is the most important indication of surgery because it has the greatest impact on prognosis.[25] Thus, moderate-to-severe CHF is an indisputable indication to perform surgery in an urgent setting. For the other indications, the optimal timing of surgery is more difficult to determine because of the lack of evidence-based data. However, since a poor surgical outcome is predicted by CHF, surgery is also recommended in patients without CHF but with an acute severe valvular regurgitation associated with elevated left end-diastolic pressures.[13] Moreover, it has been shown that the size of vegetations is a predictor of embolism and death;[17] in cases of large vegetations, the benefit of surgery might be greater in the first week of antimicrobial therapy when the risk of embolism is the highest.[19,20] Notably, a high risk of embolism is rarely the only reason for surgery, but nonetheless it suggests an earlier operation when associated with other indications.[2] In addition, recent studies have shown convincing evidence that the presence of abscesses, with or without fistulae, is associated with poor prognosis.[26]

The strength of these guidelines is limited by the absence of recommendations for the optimal timing of surgery because of a lack of evidence from prospective randomized controlled trials. In clinical practice, the benefit of operating very early should be balanced against a theoretically higher risk of perioperative death and prosthetic infection. The critical point of the timing of surgery has been poorly analysed and the few observational studies that have addressed this subject have shown conflicting results and selection bias.[27–32] Propensity analysis is a means of limiting the confounding effect of the selection bias that has been used in several recent studies that examined the impact of surgery on mortality.[6–10] Since similar potential ethical and logistical constraints do not allow us to conduct a randomized controlled trial on the impact of the timing of surgery, we also chose to perform a propensity analysis in a large group of patients. The large size of the sample served to provide meaningful data despite the fact that the investigators had had no control over the treatment assignment. Only one recent study used this methodology to examine the association between the timing of surgery and the outcome.[14] In that work, the authors did not demonstrate an independent effect of this timing on 6-month mortality after an adjustment for the PS.

Table 5 **Significant differences in patient characteristics by propensity subgroups (quintiles)**

	Propensity groups (stratified into quintiles)					*P* for trend
	Q1 (*n* = 59)	**Q2 (*n* = 57)**	**Q3 (*n* = 59)**	**Q4 (*n* = 58)**	**Q5 (*n* = 58)**	
Age (mean ± SD, years)	62 ± 12	58 ± 14	58 ± 16	56 ± 16	48 ± 17	<0.0001
Staphylococcus aureus	3 (5)	8 (14)	8 (14)	10 (17)	19 (33)	<0.0001
CHF	15 (25)	28 (49)	25 (42)	24 (41)	30 (52)	0.027
Vegetation length (median, [interquartile range], mm)	9 (3–15)	10 (0–15)	11 (4–18)	15 (6–20)	16 (10–19)	0.006
Vegetation length >10 mm	27 (46)	26 (46)	31 (53)	36 (62)	44 (76)	<0.0001
Vegetation length >15 mm	12 (20)	13 (23)	18 (31)	26 (45)	29 (50)	<0.0001

Values are expressed as number (%). CHF, congestive heart failure.

Although similar results were found in our entire cohort, the larger sample size allowed us to stratify this cohort into quintiles of equal size based on the estimated PS. Thus, selection bias could be reduced in each quintile because the patients had the same probability for undergoing ≤1st week surgery. With this design, we could define a subset of patients with an independent beneficial survival effect from the ≤1st week surgical strategy. These patients were more likely to be young and to have *S. aureus* infections, CHF, and larger vegetations. The benefit to operate very early seems to be higher than the risk when those factors are present. Thus, the present results encourage a very early operation regardless of the length of the antimicrobial treatment, when the patients have a *S. aureus* IE complicated by CHF and large vegetations. The rate of abscesses was not significantly higher in the subgroup of patients who benefit the most from a very early surgical management, probably because the number of uncomplicated abscess (without fistula) was low.

Timing of surgery and relapses or postoperative valvular dysfunctions

Relapse of IE is a serious complication since re-infection usually occurs on a prosthetic valve, although this risk is more dependent on the surgeon's ability to extirpate all infected tissues.

Some previous series have suggested that the risk of relapse depends on the time between the beginning of antimicrobial therapy and the surgery.[28] In the present study, the overall rate of relapses or PVD was 8%, which is in accordance with previous studies.[33,34] The use of propensity analysis confirmed the trend to a higher risk of relapses and/or PVD when surgery was performed very early. However, this risk should be balanced against the beneficial effect of very early surgery in the high-risk patients.

Limitations

Although the use of PS to adjust for confounding in treatment selection is intended to control for this bias, it cannot completely eliminate the effect of confounding. Our model was based only on patients' characteristics that were documented in our database, and cannot account for variables that were not collected. Thus, despite rigorous analysis, the level of evidence of our results cannot be as high as those coming from a randomized controlled study. Moreover, despite an original rigorous methodology based on stratification of patients according to their probability of undergoing ≤1st week surgery, the relatively small sample size of the quintiles, the small number of events in each quintile, and the exclusion of no operated patients because of excessive operative risk limited the interpretation of the results. Beside, we cannot exclude that patients likely to have very early surgery, but did not actually have it, had some unobserved reasons for that, related to poor outcome.

Because of these limitations, we were not able to precisely define the indications for ≤1st week surgery and we must not conclude that very early surgery is not beneficial in patients with only one indication for surgery particularly in the case of isolated large vegetation. However, for the first time, we identified a high-risk subgroup that might benefit from this strategy. To build the PS, we had to choose a cut-off for the timing of surgery. Thus, the present study could not determine the optimal time interval between the beginning of antimicrobial therapy and the surgical treatment. However, the cut-off of 7 days was chosen according to data from previous studies that showed a higher risk of embolism during this time, and a failure of medical treatment when bacteraemia persists after one week.[19,20] It should be emphasized that surgery must sometimes be performed on the day when the decision to operate is made, but this hypothesis could not be confirmed. Finally, our work was subject to a referral bias and was conducted during a long period when changes in the management of patients occurred.

Conclusion

This observational study suggests that the timing of surgery has an impact on 6-month mortality, relapses, and PVD in patients with IE. The effect on the mortality of ≤1st week surgical management is not uniform, and might be beneficial in patients with the most severe IE. However, this very early operation is expected to involve a greater risk of relapses or PVD. These preliminary results, which may help physicians to indicate very early surgery, still require confirmation by large preferably randomized studies that may more accurately define the optimal timing of surgery according to the individual patient characteristics.

Conflict of interest: none declared.

References

1. Hoen B, Alla F, Selton-Suty C, Béguinot I, Bouvet A, Briançon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi JL, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA* 2002;**288**:75–81.
2. Tornos P, Iung B, Permanyer-Miralda G, Baron G, Delahaye F, Gohlke-Barwolf Ch, Butchart EG, Ravaud P, Vahanian A. Infective endocarditis in Europe: lessons from the Euro heart survey. *Heart* 2005;**91**:571–575.
3. Cabell CH, Jollis JG, Peterson GE, Corey GR, Anderson DJ, Sexton DJ, Woods CW, Reller LB, Ryan T, Fowler VG Jr. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med* 2002;**162**:90–94.
4. Fowler VG Jr, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, Corey GR, Spelman D, Bradley SF, Barsic B, Pappas PA, Anstrom KJ, Wray D, Fortes CQ, Anguera I, Athan E, Jones P, van der Meer, Elliot TS, Levine DP, Bayer AS. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA* 2005;**293**:3012–3021.
5. Wang A, Athan E, Pappas PA, Fowler VG Jr, Olaison L, Paré C, Almirante B, Munoz P, Rizzi M, Naber C, Logar M, Tattevin P, Iarussi DL, Selton-Suty C, Jones SB, Casabé J, Morris A, Corey GR, Cabell C. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA* 2007;**297**:1354–1361.
6. Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. *JAMA* 2003;**290**:3207–3214.
7. Aksoy O, Sexton DJ, Wang A, Pappas PA, Kourany W, Chu V, Fowler VG Jr, Woods CW, Engemann JJ, Corey R, Harding T, Cabell CH. Early surgery in patients with infective endocarditis: a propensity score analysis. *Clin Infect Dis* 2007;**44**:364–372.
8. Cabell CH, Abrutyn E, Fowler VG Jr, Hoen B, Miro JM, Corey GR, Olaison L, Pappas P, Anstrom KJ, Stafford JA, Eykyn S, Habib G, Mestres SA, Wang A. Use of surgery in patients with native valve infective endocarditis: results from the International Collaboration on Endocarditis Merged Database. *Am Heart J* 2005;**150**:1092–1098.
9. Wang A, Pappas P, Anstrom KJ, Abrutyn E, Fowler VG Jr, Hoen B, Miro JM, Corey GR, Olaison L, Stafford JA, Mestres CA, Cabell CH. The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort. *Am Heart J* 2005;**150**:1086–1091.
10. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, Hoskin TL, Mirzoyev Z, Anavekar NS, Enders F, Moustafa S, Mookadam F, Huskins C, Wilson W, Baddour LM. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. *Circulation* 2007;**115**:1721–1728.

11. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G, von Graevenitz A. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary: the task force on infective endocarditis of the European Society of Cardiology. *Eur Heart J* 2004;**25**:267–276.
12. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani Ly, Gewitz MH, Tong DC, Steckelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TJ, Takahashi M, Taubert KA. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005;**111**:e394–e434.
13. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006;**48**:e1–e148.
14. Tleyjeh IM, Steckelberg JM, Georgescu G, Ghomrawi HM, Hoskin TL, Enders FB, Mookadam F, Huskins WC, Wilson WR, Baddour LM. The association between the timing of valve surgery and six-month mortality in left-sided infective endocarditis. *Heart* 2008;**94**:892–896.
15. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;**30**:633–638.
16. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802.
17. Thuny F, Di Salvo G, Belliard O, Avierions JF, Pergola V, Rosenberg V, Casalta JP, Gouvernet J, Derumeaux G, Iarussi D, Ambrosi P, Calabro R, Riberi A, Collart F, Metras D, Lepidi H, Raoult D, Harle JR, Weiller PJ, Cohen A, Habib G. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation* 2005;**112**:69–75.
18. Daniel WG, Mugge A, Martin RP, Lindert O, Hausmann D, Nonnast-Daniel B, Laas J, Lichtlen PR. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. *N Engl J Med* 1991;**324**:795–800.
19. Steckelberg JM, Murphy JG, Ballard D, Bailey K, Tajik AJ, Taliercio CP, Guiliani ER, Wilson WR. Emboli in infective endocarditis: the prognostic value of echocardiography. *Ann Intern Med* 1991;**114**:635–640.
20. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, Doco-Lecompte T, Eisen DP, Fortes CQ, Fowler VG Jr, Lerakis S, Miro JM, Pappas P, Peterson GE, Rubinstein E, Sexton DJ, Suter F, Tornos P, Verhagen DW, Cabell CH, ICE Investigators. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE prospective cohort study (ICE-PCS). *Am Heart J* 2007;**154**:1086–1094.
21. D'Agostino RB Jr. Propensity scores methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;**17**:2265–2281.
22. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984;**79**:516–524.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–383.
24. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2001;**345**:1318–1330.
25. Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. *JAMA* 2003;**289**:1933–1940.
26. Anguera I, Miro JM, Cabell CH, Abrutyn E, Fowler VGJ, Hoen B, Olaison L, Pappas PA, de Lazzari E, Eykyn S, Habib G, Pare C, Wang A, Corey R. Clinical characteristics and outcome of aortic endocarditis with periannular abscess in the International Collaboration on Endocarditis Merged Database. *Am J Cardiol* 2005;**96**:976–981.
27. Olaison L, Hogevik H, Myken P, Oden A, Alestiq K. Early surgery in infective endocarditis. *Quart J Med* 1996;**89**:267–278.
28. Aranki SF, Santini F, Adams DH, Rizzo RJ, Couper GS, Kinchla NM, Gildea JS, Collins JJ Jr, Cohn LH. Aortic valve endocarditis. Determinants of early survival and late morbidity. *Circulation* 1994;**90**:II175–II182.
29. Hill EE, Herregods MC, Vanderschueren S, Claus P, Peetermans WE, Herijgers P. Outcome of patients requiring valve surgery during active infective endocarditis. *Ann Thorac Surg* 2008;**85**:1564–1570.
30. Middlemost S, Wisenbaugh T, Meyerowitz C, Teeger S, Essop R, Skoularigis J, Cronje S, Saleri P. A case for early surgery in native left-sided endocarditis complicated by heart failure: results in 203 patients. *J Am Coll Cardiol* 1991;**18**:663–667.
31. Alexiou C, Langley SM, Stafford H, Lowes JA, Livesey SA, Monro JL. Surgery for active culture-positive endocarditis: determinants of early and late outcome. *Ann Thorac Surg* 2000;**69**:1448–1454.
32. Revilla A, Lopez J, Vilacosta I, Villacorta E, Rollan MJ, Echevarria JR, Carrascal Y, Di Stefano S, Fulquet E, Rodriguez E, Fiz L, San Roman JA. Clinical and prognostic profile of patients with infective endocarditis who need urgent surgery. *Eur Heart J* 2007;**28**:65–71.
33. Renzulli A, Carozza A, Romano G, De Feo M, Della Corte A, Gregorio R, Cotrufo M. Recurrent infective endocarditis: a multivariate analysis of 21 years of experience. *Ann Thorac Surg* 2001;**72**:39–43.
34. David TE, Gavra G, Feindel CM, Regesta T, Armstrong S, Maganti MD. Surgical treatment of active infective endocarditis: a continued challenge. *J Thorac Cardiovasc Surg* 2007;**133**:144–149.